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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/316,199 | 05/21/1999 | Michael J McCluskie | C1040/7006HC | 7506 |

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| EXAMINER | |
|---|---|
| NGUYEN, DAVE TRONG | |
| **ART UNIT** | **PAPER NUMBER** |
| 1632 | |

DATE MAILED: 02/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/316,199 | MCCLUSKIE ET AL. | |
| | Examiner | Art Unit | |
| | Dave T Nguyen | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *24 November 2003*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-28 and 125-130* is/are pending in the application.

4a) Of the above claim(s) *11,13 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,12,14-22,24-28 and 125-130* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/24/03 &11/99*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claim 9 has been amended by the response filed November 20, 2003.

Claims 11, 13, 23 remain withdrawn from consideration as being drawn to a non-elected species.

Elected claims 1-10, 12, 14-22 and 24-28 readable on species of 5' X1X2CGX3X4 3' wherein X1 is G, X2 is T, X3 is T, and X4 is T as a species of CpG motif, the species of colloidal dispersion system, the species of alum as non-oligo mucosal adjuvant, the species of subject at risk of developing an infectious disease, the species of infectious virus as a species of antigen, the species of intranasal route, to which the following grounds of rejection are applicable, are pending.

The species AACpGTT has been rejoined for examination given a prior art submitted in the latest IDS reads on the rejoined species.

The IDS (dated November 20, 2003) citing pending US filed application has been considered by the examiner.

PTO-1449 submitted November 10, 2003 and resubmitted PTO-1449 (dated 11/99) also have been considered by the examiner, and is attached to this office action.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10, 12 and 14-22, 24-28, 125-130 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inducing a mucosal immune response, comprising:

Administering to a mucosal surface of a subject an effective amount for inducing a mucosal immune response of an oligonucleotide having a length of least 8 nucleotide residues and comprising CpG motif containing oligonucleotide including the elected species of 5' X1X2CGX3X4 3', wherein both C and G are unmethylated; and administering to the subject an antigen not encoded in a nucleic acid vector to the subject, thereby inducing the mucosal immune response, does not reasonably provide enablement for methods of administering any CpT motif containing oligonucleotide of less than 8 nucleotide residues including the elected species of 5' X1X2CGX3X4 3' wherein X1 is G, X2 is T, X3 is T, and X4 is T for inducing a mucosal immunity to a recombinant peptide/polypeptide antigen within the context of therapeutic applications. The as-filed specification is also not enabling for a method of inducing a mucosal immunity wherein the subjected treated with the oligonucleotide is just simply passively waited for any period of to time to be exposed to an antigen which is not encoded in a nucleic acid vector.

With respect to the preamble of claim 1 and claims dependent therefrom,

the presently pending claims encompass a method of "exposing" any subject including mammals, insects, reptiles, birds that is at risk of developing an infectious disease, *e.g.,* viral infection, it is apparent to a skilled artisan on the basis of applicant's disclosure that in order to carry out the invention, the administered nucleic acid or oligo containing a CG motif must necessarily by itself induces a sufficient mucosally therapeutic response at any subsequent period at which the treated subject is simply passively exposed to an antigen, *e.g.,* by simply inhalation or eating or skin contact, for example. No working examples are provided for this particular claimed embodiment. No data from either the as-filed specification or the prior art are provided to illustrate this particular embodiment. As evidenced by numerous arts cited in the IDS, for example all of the publications authored by Heather Davis or McCluskie, teach that CpG (wherein both CG are unmethylated) containing oligos are known to be an effective adjuvant when administered together with a sufficient amount of antigen or shortly prior or after an active administration of an effective dose of antigen, and that oligos are not simple drugs and intrinsically posses degradation properties in an in vivo environment. Furthermore, at about the filing date of the present application, both Krieg et al. (Trends in Microbiology 6:23-27, 1998; IDS) and McCluskie et al. (Crit. Rev. Immunol. 19:303-329, 1999) have noted that the route of administration and DNA dose (for this instance, oligonucleotides having the recited core structure) as well as other factors such as the antigen, the dose of antigen, the co-expression of cytokines, and whether other adjuvant is used are also involved in determining the types of host immune responses elicited

(page 313, see the section titled "Role of CpG immunostimulatory sequences).

The doubts expressed in the art of record are further substantiated by HL Davis (Curr Top Microbiol Immunology, 247, 171-83, 2000, IDS). HL Davis clearly teaches (page 179, second full par.) that even with CpG ODN with a phosphate backbone modification, the ODN are "apparently not sufficiently nuclease resistant to exert a strong CpG-adjuvant effect". This would reasonably shows that use of CpG ODN with a phosphate backbone modification as an adjuvant in combination with an administered co-antigen is not "useful", and further suggests that its use as a prophylactic drug remains problematic and is not reasonably predictable. HL Davis on the same par. further states that even with an administered DNA vaccine that is employed at the same time as the modified CpG ODN but is administered at a different site in a subject, the administered CpG will not augment responses to the administered DNA vaccines. This also further suggests that prophylactic uses of CpG ODNs are not routine and remains problematic, especially in the absence of evidence to the contrary. Another equally important issue that further substantiate the unpredictability of employing a CpG motif for prophylactic use in a mammal other than mice is the disclosure in McCluskie, Vaccine, 231-237, 2000, IDS), which teaches (page 237) that the studies presented in mice with respect to CpG 's role in inducing a mucosal immunity do not predict the situations in humans as another exemplified mammal or subject, and that there are differences in the murine and human respiratory systems. More specifically, McCluskie states:

Mucous-secreting surface epithelial cells which are found throughout the

tracheobronchial epithelium of humans are rare in rodents beyond the trachea, and mucous glands are found in human but rodent airways [35]. In addition, most larger mammals, including humans, possess palatine, lingual and pharangeal tonsils, which act as the major inductive mucosal immune responses in the respiratory tract [36]. In contrast, rodents lack pharyngeal and palatine tonsils and instead possess bilateral strips of lymphoid tissue underlying the respiratory epithelium of the nasal cavity and the nasopharynx [37, 38]. It will be desirable to carry out studies using CpG DNA as a mucosal adjuvant on other mammals such as sheep, ferrets or nonhuman primates, where the pulmonary epithelium is more similar to that of humans.

The references in addition with other cited references, when considered as a whole, suggest convincingly that prophylactic use of any of the claimed CpG ODN is real world subjects other mice remains complex, and that the murine model does not appear to be an art-recognized model for prophylactic application of a CpG ODN to raise a mucosal immunity that is sufficient to treat any subject exposed subsequently to an antigen at any *in vivo* site passively or actively.

As such, given the complexity and variable factors that interplay during an administration of a CpG motif containing oligonucleotide, and given the breadth of the claimed invention, wherein the claimed oligo can be reasonably interpreted as a preventive drug for immunization in any subject so as to elicit any preventive response to any passive exposure by any subject to an allergen or antigen, it is not apparent how a skilled artisan to determine, without any undue experimentation, as to which particular among an enormous number of claimed

oligos, and/or as to which particular antigen and/or method steps can be used effective so as to generate a prophylactically mucosal response as contemplated by applicants at the time the invention was made, particularly when considered all o the Wands factors as a whole.

With respect to the breadth of the claimed invention which clearly embraces any oligonucleotide wherein only C is need to be unmethylated when present in the CG dinucleotide, the totality of the prior art (also cited by the IDS, which includes McCluskie references, Krieg references, and Davis references and issued patents authored by any of the mentioned authors) clearly teach that CpG motifs are needed to be unmethylated, and that the unmethylated CpG containing oligo of at least 8 nucleotides and its flanking residues are critical for is immunostimulatory activity, let alone its specifically claimed mucosal immunostimulatory activity. McCluskie (1998, The J. of immunology, 161:4463-4466) and Moldoveanu (Vaccine 16, 1216, 1998) are cited to illustrate the importance of the presence of CpG motif wherein both C and G nucleotides are unmehtylated) in order to elicit an mucosal immunity when administered together with a recombinant antigen.

Accordingly, due to the lack of guidance provided by the specification regarding to the issues set forth above, the unpredictability of the physiological, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

Applicant's response filed November 20, 2003 has been considered by the

examiner but is only found partially persuasive. Applicant's response with respect to the routes of administration has been considered and is found persuasive. As such, the issue with respect to the routes of administration embraced by the enabling embodiments, drawn to therapeutic or adjuvant applications of the CpG motifs containing oligos, has been withdrawn from the stated rejection.

With respect to the issue of "exposing the subject to an antigen that is not encoded in a nucleic acid vector", which has been reasonably interpreted by the examiner as embracing the use of applicant's CpG motif containing oligos as essentially prophylactic drugs: a method of employing a CpG containing motif for mucosal administration so as to enhance a mucosal immunity in any subject at risk of being "exposed" actively or passively to an antigen such as infectious agents (HIV viruses, tumor antigen), applicant's response has been considered by the examiner but is not found persuasive because of the reasons set forth on the record. Applicant mainly asserts that given the guidance provided by the specification, the teaching provided by one of applicant's copending application (09/241,653), the points or issue raised in the stated office action is not correct. However, the examiner notes that the stated office action clearly has provides a number of reasoning demonstrating that neither the adjuvant's property of a CpG motif containing oligos nor its therapeutic applications is not the same as preventive treatments of utilizing CpG oligos to induce an effective amount of a musosal immunity so as to treat prophylactically any subject that is exposed either passively or actively to an antigen at any period of time. The fact that the

application provides guidance that does nor provide any substantial evidence to overcome the doubts expressed in the art of record is not the same as enabling for the full breadth of the presently pending claims. The doubts expressed in the art of record are further substantiated by HL Davis (Curr Top Microbiol Immunology, 247, 171-83, 2000, IDS). HL Davis clearly teaches (page 179, second full par.) that even with CpG ODN with a phosphate backbone modification, the ODN are "apparently not sufficiently nuclease resistant to exert a strong CpG-adjuvant effect". This would reasonably shows that use of CpG ODN with a phosphate backbone modification as an adjuvant in combination with an administered co-antigen is not "useful", and further suggests that its use as a prophylactic drug remains problematic and is not reasonably predictable. HL Davis on the same par. further states that even with an administered DNA vaccine that is employed at the same time as the modified CpG ODN but is administered at a different site in a subject, the administered CpG will not augment responses to the administered DNA vaccines. This also further suggests that prophylactic uses of CpG ODNs are not routine and remains problematic, especially in the absence of evidence to the contrary. Another equally important issue that further substantiate the unpredictability of employing a CpG motif for prophylactic use in a mammal other than mice is the disclosure in McCluskie, Vaccine, 231-237, 2000, IDS), which teaches (page 237) that the studies presented in mice with respect to CpG 's role in inducing a mucosal immunity do not predict the situations in humans as another exemplified mammal or subject, and that there are differences in the murine and human respiratory

systems. More specifically, McCluskie states:

Mucous-secreting surface epithelial cells which are found throughout the tracheobronchial epithelium of humans are rare in rodents beyond the trachea, and mucous glands are found in human but rodent airways [35]. In addition, most larger mammals, including humans, possess palatine, lingual and pharangeal tonsils, which act as the major inductive mucosal immune responses in the respiratory tract [36]. In contrast, rodents lack pharyngeal and palatine tonsils and instead possess bilateral strips of lymphoid tissue underlying the respiratory epithelium of the nasal cavity and the nasopharynx [37, 38]. It will be desirable to carry out studies using CpG DNA as a mucosal adjuvant on other mammals such as sheep, ferrets or nonhuman primates, where the pulmonary epithelium is more similar to that of humans.

The references in addition with other cited references, when considered as a whole, suggests convincingly that prophylactic use of any of the claimed CpG ODN is real world subjects other mice remains complex, and that the murine model does not appear to be an art-recognized model for prophylactic application of a CpG ODN to raise a mucosal immunity that is sufficient to treat any subject exposed subsequently to an antigen at any *in vivo* site passively or actively.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-10, 12, 14-22, 26-28, 125-130 are rejected under 35 U.S.C. 102(e) as being anticipated by Carson (US 20030109469, IDS submitted after the non-final office action), as evidenced by Moldoveanu *et al.,* Vaccine 16, p. 1216, 1998, McCluskie *et al.* (IDS, C2), and McCluskie (Vaccine 18, 413-422, 2001).

The essential feature of the presently pending claims is that a mucosal immunity would be elicited by a combination administration to the mucosal surface of any subject, *e.g.,* intranasal or inhaled administration, of any known antigen (not in the form of a nucleic acid sequence) and an oligonucleotide (which can be a nucleic acid vector comprising a CpG motif in the non-coding sequence complexed with any known colloidal dispersion system including lipid based system) having a length of least 8 nucleotide residues and comprising CpT motif containing oligonucleotide including the elected species of 5' X1X2CGX3X4 3' wherein X1 is A, X2 is A, X3 is T, and X4 is T. Carson *et al.* teach the same throughout the disclosure (abstract, claim

25, paragraphs 0012, 0016, 0041, 0044, 0049, 0112, 0128, 0129, and 0139). More specifically, on par. 0139, inhalation administration and nasal administration of the oligo and/or antigen is disclosed. The use of a colloidal dispersion system is disclosed on par. 0074-0075. In view of the factual evidence established by Moldoveanu *et al.,* Vaccine 16, p. 1216, 1998, McCluskie *et al.* (IDS,. C2), and McCluskie (Vaccine 18, 413-422, 2001)which shows that CpG motifs when administered to the mucosal surface of a subject does generate an mucosal immunity, the method of Carson, which is identical to that of the claimed embodiments embraced by the presently pending claims, would generate production of mucosal immunity, particularly in view of the absence of evidence to the contrary.

Claims 1-10, 12, 14-22, 24-28, 125-130 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carson (US 20030109469, IDS submitted after the non-final office action) taken with Krieg *et al.* (US Pat No. 6,218,371).

To the extent that the claims embrace the use of a GTCpGTT species and/or a cytokine such as B7 costimulatory molecule in order to stimulate an immune response in a subject, Carson is applied here as indicated above. Carson neither teaches the GTCpGTT motif nor a combination use of a B7 costimulatory effect in order to provide an additive immunological effect to an antigen.

However, the use of a X1X2CpGTT, wherein X1 and X2 is any nucleotide, as an effective CpG motif to stimulate an immune response is well known in the prior art, as exemplified in Krieg throughout the disclosure. More specifically, on column 31, oral administration and nasal administration of the oligo and/or antigen is

disclosed. CpG motifs including 5' GTCpGTT is also disclosed on columns 3, 4 and 23. The use of a cytokine including B-7 as an adjuvant in combination with the CpG containing oligo of at least 8 nucleotides is disclosed on column 25, 26 and 29, for example.

It would have been obvious for one of ordinary skill in the prior art to employ any of the knownCpG motif according to the formula disclosed in Krieg in the method of Carson. One would have been motivated to do so as a minor modification or equivalent design, since Krieg teaches that X1X2CpGTT, wherein X1 and X2 can be any nucleotide, which includes the GTCpGTT motif, is an effective immunostimulatory molecule.

In addition, one of ordinary skill in the art would have been motivated to employ a combination use if any adjuvant or costimulatory molecule such as B7 in the method of Carson. One would have been motivated to do so because Krieg teaches the use of a cytokine including B-7 as an adjuvant in combination with the CpG containing oligo of at least 8 nucleotides.

Thus, the claimed invention was *prima facie* obvious.

Applicant's response states that the submitted 131 Declaration is sufficient to overcome the above 103 rejection. The Declaration including the exhibits have been considered by the examiner but is not found persuasive because of the new ground of rejection, as stated above, and because of the fact neither the papers attached to the Declaration nor the Declaration itself provide any factual evidence that the combination use of cytokine including B-7 as an adjuvant in combination with the

CpG containing oligo of at least 8 nucleotides was conceived of and reduced to practice prior to the effective filing date of US 6,21,371. The declaration and the exhibits also do not provide any substantial evidence demonstrating that the use of the GTCpGTT as an adjuvant was conceived of and reduced to practice prior to the effective filing date of US 6,21,371.

Claims 1-10, 12, 14-22, 26-28, and 125-130 are rejected under 35 U.S.C. 103(a) as being unpatentable over Briles et al. (U.S. Patent No. 6,042,838) in view of Carson (US 20030109469, IDS submitted after the non-final office action) taken with Krieg *et al.* (WO96/02555).

Briles et al. disclose an immunogenic composition and a method for eliciting an immunological response against pneumococcal surface protein A (PSPA) in a host susceptible to *Streptococcus pneumoniae* by intranasally administering to the host an effective amount of PSPA in the form of a killed whole pneumococci, a lysate of pneumococci or an isolated PSPA or an immunogenic fragment thereof in the presence of an adjuvant, with cholera toxin B as a preferred adjuvant, to protect a host against pneumoccocal colonization and/or systemic infection (see summary of invention, col. 1-7). Briles et al. also teach that immunostimulatory agents or adjuvants have been used to improve the host immune responses to vaccines, these include intrinsic adjuvants such as lipopolysaccharides which normally are the components of the killed or attenuated bacteria used as vaccines or extrinsic adjuvants such as aluminum hydroxide, LPS, Freund's complete adjuvant and others which are

immunomodulators which are typically non-covalently linked to antigens and are formulated to enhance the host immune responses. Briles further disclose that the immunogenic composition can be prepared as inhalables, sprays and that pump spray or nasal spray or squeeze dispensers (a device) for dispensing a metered dose or a dose with a particular particle or droplet size are commercial available for mucosal administration (col. 3, lines 32-52). Briles et al. further teach that useful surfactants for the immunogenic composition include polyoxyethylene derivatives of fatty acid partial esters of sorbitol anhydrides such as Tween 80, Polyoxyl 40 Stearate and others to enhance absorption (col. 6, lines 14-21). Briles et al. further teach that specific IgA antibodies are induced in secretions of the intestinal, respiratory, and genital tracts, as well as predominantly IgA antibody secreting cells in the intestinal lamina propria and salivary glands. Strong circulatory immune responses are also induced with IgG and IgA antibodies in the serum, and IgG and IgA antibody-secreting cells in the spleen (col. 8, lines 14-34, and examples). Briles et al. do not teach the use of any immunostimulatory oligonucleotide, including a core nucleotide sequence having the formula: 5'-Purine-Purine-[C]-[G]-Pyrimidine-Pyrimidine-3' or one having the core nucleotide sequence of the elected species as an adjuvant in a composition or a method for inducing mucosal immunity to an antigen in a mammalian host via intranasal administration.

However, at the effective filing date of the present application, Carson teaches that a mucosal immunity would be elicited by a combination administration to the mucosal surface of any subject, *e.g.*, intranasal or inhaled

administration, of any known antigen (not in the form of a nucleic acid sequence) and an oligonucleotide (which can be a nucleic acid vector comprising a CpG motif in the non-coding sequence complexed with any known colloidal dispersion system including lipid based system) having a length of least 8 nucleotide residues and comprising CpT motif containing oligonucleotide including the elected species of 5' X1X2CGX3X4 3' wherein X1 is A, X2 is A, X3 is T, and X4 is T. Carson *et al.* teach the same throughout the disclosure (abstract, claim 25, paragraphs 0012, 0016, 0041, 0044, 0049, 0112, 0128, 0129, and 0139). More specifically, on par. 0139, inhalation administration and nasal administration of the oligo and/or antigen is disclosed. The use of a colloidal dispersion system is disclosed on par. 0074-0075.

In addition, the use of a X1X2CpGTT, wherein X1 and X2 is any nucleotide, as an effective CpG motif to stimulate an immune response is well known in the prior art, as exemplified in Krieg throughout the disclosure. Krieg et al. disclose various immunostimulatory oligonucleotides having the CpG motifs, among which is an oligonucleotide comprising the sequence AACpGTT (see Table 1). For facilitating uptake into cells, the immunostimulatory oligonucleotides are preferably in the range of 8 to 40 base pairs in size (col. 6, lines 18-20). Additionally, Krieg et al. teach that the immunostimulatory oligonucleotides can be used in conjunction with a vaccine or an antigen in a pharmaceutically acceptable carrier, as an adjuvant to boost a mammal's immune response to effect better response from the vaccine (col. 17, line 65 continues to line 3 of col. 18; and the claims).

Accordingly, it would have been obvious for an ordinary skilled artisan, to modify the immunogenic composition (including a kit that has pump spray or nasal spray or squeeze dispensers for dispensing a metered dose or dose with a particular size of the immunogenic composition) and the method for inducing mucosal immunity against pneumococcal colonization and systemic infection taught by Briles et al. by utilizing an immunostimulatory oligonucleotide having the CpG motif as taught by Carson taken with Krieg in either a free form or in a non-covalently linkage with PSPA antigens as an adjuvant (It is noted that it is well known in the art of vaccine that antigen is normally conjugated to an adjuvant to enhance the host immune response as also evidenced by the teachings of Briles et al.) . One of ordinary skilled artisan would have been motivated to carry out the above modification simply because Carson clearly teach that an immunomodultory oligonucleotide having a CpG motif can be used in conjunction with a vaccine or an antigen in a pharmaceutically acceptable carrier, as an adjuvant to boost a mucosal response to effect better response from the vaccine.

It would have been obvious for one of ordinary skill in the prior art to employ any of the known CpG motif according to the formula disclosed in Krieg in the method of Briles taken with Carson. One would have been motivated to do so as a minor modification or equivalent design, since Krieg teaches that X1X2CpGTT, wherein X1 and X2 can be any nucleotide, which includes the GTCpGTT motif, is an effective immunostimulatory molecule.

Thus, the claimed invention was *prima facie* obvious.

Applicant's response with respect to the previously cited prior art rejections is moot in view of the new grounds of the rejection. Note that the new grounds of the rejections clearly set forth evidence, which shows that the concept of employing a CpG motif ODN to stimulate a mucosal immunity is known in the prior art at the time the invention was made.

Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on November 20, 2003 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609(B)(2)(i). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(571-272-0731**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Amy Nelson*, may be reached at **571-272-0184**

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Trong Nguyen
Primary Examiner
Art Unit: 1632

DAVE T. NGUYEN
PRIMARY EXAMINER